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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/528,682	PIZZA ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/08/2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-32* is/are pending in the application.

4a) Of the above claim(s) *30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/08/05 has been entered[1].

Status of the claims

2. Claims 7-32 are pending.

Pursuant to previously filed response to election of species (filed 02/25/2003), polynucleotides that encode polypeptide numbered relative to SEQ ID No. 1 are elected. Claims 30-32 remain withdrawn from consideration as drawn to non-elected species[2]. Note that claim 30 was been previously written as an exact duplicate of claim 7, but is in withdrawn status now, after it has been amended to cancel particular 8-mere sequences.

Drawings

3. It is noted that the previous Office actions objected the proposed drawing Fig. 12, as well as correspondent amendments to specification, because it introduced new

[1] On 02/08/05 applicant submitted copies of previous responses of 11/09/04 and 12/15/04, as well as amendment to specification.
[2] It seems that applicant is in error indicating that claims 20-32 are withdrawn from consideration. If withdrawal of these claims is indeed the applicant's intention, please confirm it.

matter. The original disclosure does not support the showing of sequences as resented on Fig. 12.

As stated previously, Examiner disagrees with applicant's arguments on this matter for the following reasons:

First, Domenighini reference is not incorporated into instant disclosure as incorporated by reference. Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph.

Second, nowhere in specification applicant indicated possession of mutants of the particular sequences described in the Domenighini reference. The Domenighini reference itself is used in specification not to direct to particular sequences, but to direct to one particular residue of interest that this suggestion suggests to mutate. The disclosure as filed addresses strains of LT in general (p. 5, lines 5-7) and does not reduce the genus to particular species addressed in Domenighini.

Third, even if it had been incorporated by reference, information on SEQ ID Nos 1-4 presented in the reference is essential material as it is being directly claimed in the amended claims. "Essential material" may not be incorporated by reference to non-patent publications. See MPEP 608.01(p). Further, there is nothing in the specification as filed suggesting LT-A sequences having residues other than Ala at position 72, whereas SEQ ID Nos 3,4 on the figure present proteins with different residues (I and L) therein.

Specification

4. The amendment filed 02/08/2005 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The listing of sequences SEQ ID Nos. 1-4 constitutes new matter for the same reasons as their description in the form of Fig. 12 – see the preceding objection to the Drawings.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 U.S.C. § 112, first paragraph.

5. Claims 7-29 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims recite 8-meres of SEQ ID No. 1. The specification as filed addressed fragments of LT-A in general, but have not addressed fragments of particular size as now claimed.

Applicant submits that "the octapeptide recitations have been removed from the claims". This is not correct. Recitation of particular sequences has been removed from the claims but the claims remain to be directed to fragments of particular length, of 8-meres and more, that has not been disclosed in specification as filed. Examiner maintains that the claims have not addressed particular species, fragments of particular size of particular SEQID No. 1. All that is described in specification as filed are fragments of LT-A in general. See MPEP 2163.05:

The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original).

Note that all Domenighini reference was used for - in the much recited section of specification (p. 5, lines 25+) - is to point at location of Ala residue in a particular location. Nowhere does specification as filed demonstrates possession of fragments of particular size of particular sequence, SEQ ID No. 1.

6. Claims 7-29 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification as filed addresses polynucleotides encoding full-length subunits of LT-A (p.7, lines 23-26) but does not describe polynucleotides encoding any other polypeptides comprising certain fragments of LT-A.

Applicant argues that the "fifth aspect of invention" reads includes fragments of a protein. However, as stated in specification:

> According to a fifth aspect of the invention, there is provided a DNA sequence encoding an immunogenic detoxified protein according to the first aspect of the invention.

In turn, the "first aspect" as correctly cited by the applicant is drawn to protein or its fragments. The specification does not define the protein as being "a protein or its

fragments"; rather it addresses protein on its own and then continues that the invention is also drawn to fragments of said protein. Thus, the "fifth aspect", the DNA encoding protein, reads on DNA encoding full-length protein, but not on DNA encoding any other polypeptides comprising certain fragments of the protein. Specification neither demonstrates possession of polypeptides comprising certain fragments of particular size of particular sequence, SEQ ID No. 1, nor nucleic acids encoding therefor.

7. Claims 7-29 remain rejected under 35 U.S.C. 112, first as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims as amended are drawn to polynucleotides encoding polypeptides comprising immunogenic fragments of LT-A comprising at least eight residues and containing Arg in position corresponding to Ala72. Prior art teaches that LT-A derivatives having Arg72 remained to be toxic. See WO 93/13202, p. 46, line 51, or Pizza, 1993, p. 93, left column, last paragraph. The instant application demonstrates that full length LT-A has reduced toxicity as compared to wild-type, (Figs 4,5), but does not demonstrate any octamers of LT-A that are detoxified compared to wild type LT-A. Further, there is no description in the claims or specification sufficiently identifying epitope sequence. Consequently, there is no guidance on what fragments are required to maintain immunogenecity of the fragments required by the claims. Accordingly, there are no sufficient structural characteristics for DNA encoding thereof,

and correspondent vectors, and host cells and one skilled in the art would not know how to make the invention as claimed without undue experimentation.

Applicant argues by citing general methods of making and testing peptide fragments, but fails to demonstrate existence of at least one "detoxified" fragment.. Examiner maintains that given the absence of any octamers of LT-A that are detoxified compared to wild type LT-A, lack of guidance of what core structure is required for the fragments to have biological activity as claimed, and lack of predictability in prior art, one skilled in the art would not know how to make the invention as claimed without undue experimentation.

Applicant submits that the prior art references submitted to demonstrate toxicity of fragments with replaced Ala-72 are "entirely irrelevant" as long as applicant pointed out which residue (Ala-72) is to be mutated. Examiner disagrees. The instant application demonstrates that full length LT-A has reduced toxicity as compared to wild-type, (Figs 4,5), but does not demonstrate any octamers of LT-A that are detoxified compared to wild type LT-A. Prior art, on the other side, teaches that LT-A derivatives having Ala72 replaced with Arg72 remain to be toxic. Further, there is no description in the claims or specification sufficiently identifying epitope sequence. Consequently, there is no guidance on what fragments are required to maintain immunogenecity and, at the same time, possess reduced toxicity.

Claim Rejections - 35 USC § 102 and 103.

8. Claims 7-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over EP 145486.

The patent teaches compositions and vaccines comprising modified LT-A of the following original sequences, respectively:

1 MKNITFIFFI LLASPLYANG DRLYRADSRP PDEIKRSGGL MPRGHNEYFD
51 RGTQMNINLY DHARGTE**TGF VRYDDG**YVST SLSLRSAHLA GQFILSGYST
101 YYIYVIATAP NMFNVNDVLG VYSPHPYEQE VSALGGIPYS QIYGWYRVNF
151 GVIDERLHRN REYRDRYYRN LNIAPAEDGY RLAGFPPDHQ AWREEPWIHH
201 APQGCGNSSR TITGDTCNEE TQNLSTIYLR EYQSKVKRQI FSDYQSQVDI

The referenced protein comprises sequence TGFVRYDDG (underlined), which is a fragment of subunit LT-A having Arg residue instead of Ala. The only meaning that Examiner reads into the limitation that the fragment comprises "amino acids residue corresponding to Ala-72 of SEQ ID No. 1" is that the residue which is being replaced as claimed has to be a residue corresponding to Ala,, i.e., it has to be any Ala replaced by any, in this case, Arg residue. Any Ala residue will be "corresponding" to any other Ala residue because they are the same by their nature.

As the referenced protein presents a practical interest, as it can be used as an immunogenic stimulant and vaccine, one would be motivated to produce such protein recombinantly using conventional methods of molecular biology. Further, in regard to the second immunogenic component, because combination therapies for generation of immune response are well-known in the art and because it would have been desirable to use plural therapies in order to maximize the effectiveness of the treatment, it would be *prima facie* obvious to one of ordinary skills in the art at the time the invention was

made to be motivated to use the immunogenic subunit LT-A in combination with another immunogenic antigen. Modification to combine components all known to be useful as immunogenic agents would have been obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be useful for the very same purpose. Consequently, it would have been obvious to produce such conjugate protein recombinantly using conventional methods of molecular biology.

9. Claims 7-29 remain rejected under 35 U.S.C. 102(b) as anticipated by Burnette et al (US Patent 5,770,203).

The reference teaches nucleic acid (SEQ ID No. 1) encoding cholera toxin, modified cholera toxins, nucleic acids, vectors and host cells corresponding thereto. The toxin comprises fragment 29-54 of the instantly claimed SEQ ID No. 1 (see sequence alignment attached to the action mailed 09/15/2004), said fragment containing a plurality of Arg residues (see, e.g., residues 33, 54). Therefore, the reference teaches nucleic acid encoding fragment of LT-A containing Arg residue. Although the reference does not teach that the Arg residue originated from a replacement of an Ala residue, the referenced product satisfies the structural limitation of instant claim to contain an Arg residue. As to the description of the location of (nonexistent) Ala residue, the only meaning that Examiner reads into the limitation that the claimed product contains Arg residue which is located in place where any Ala residue might have been located as well.

10. This is an RCE of applicant's earlier Application No. 09/528682. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

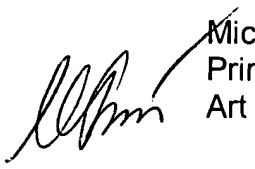
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb